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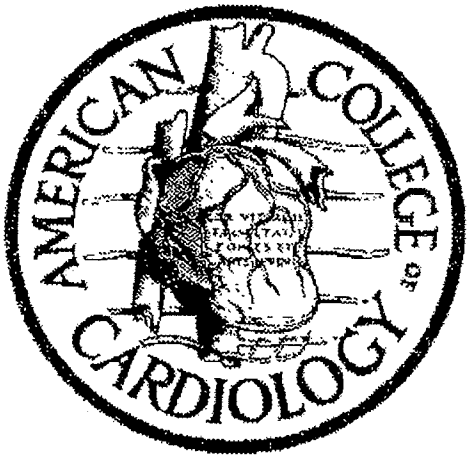

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Ineffectiveness of Colchicine for the Prevention of Restenosis After Coronary Angioplasty

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Colchicine, an antimitogenic agent, has shown promise in preventing restenosis after coronary angioplasty in experimental animal models. A prospective trial was conducted involving 197 patients randomized in a 2:1 fashion to treatment with oral colchicine, 0.6 mg twice daily (130 patients), or placebo (67 patients) for 6 months after elective coronary angioplasty. Treatment in all patients began between 12 h before angioplasty and 24 h after angioplasty. Compliance monitoring revealed that 96% of all prescribed pills were ingested. Demographic characteristics were similar in colchicine- and placebo-treated groups. A mean of 2.7 lesions/patient were dilated. Side effects resulted in a 6.9% dropout rate in the colchicine-treated patients.

Complete quantitative angiographic follow-up was obtained in 145 patients (74%) with 393 dilated lesions. Quantitative angiographic measurements were obtained in two orthogonal views at baseline before angioplasty and immediately and at 6 months after angioplasty. The quantitative mean lumen diameter stenosis before angioplasty was 67% both in the 152 lesions in the placebo-treated group and in the 241 lesions in the colchicine-treated group; this value was reduced to 24% immediately after angioplasty in the lesions in both treatment groups.

At the 6-month angiogram, lesions had restenosed to 47% lumen diameter narrowing in the placebo-treated group compared with 46% in the colchicine-treated group (p = NS). Forty-one percent of colchicine-treated patients developed restenosis in at least one lesion compared with 45% of the placebo-treated group (p = NS). In conclusion, colchicine was ineffective for preventing restenosis after coronary angioplasty.

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All currently available methods for percutaneous coronary revascularization (including balloon dilation, atherectomy, laser photoablation and intraluminal stenting) cause significant endovascular trauma. The subsequent reparative response involves myointimal proliferation that results in a significant renarrowing or restenosis in 30% to 40% of lesions by 6 months after angioplasty (1). The stimuli for the smooth muscle cell proliferation involve mechanical and rheologic factors in addition to heterogeneous growth factors emanating from inflammatory cells and elements of the coagulation system (2,3). The majority of restenosis trials performed to date have attempted to modify a single component of this complex redundant system. The failure of any single pharmacologic agent to consistently reduce the restenosis rate after coronary angioplasty is somewhat predictable in this context.

This exuberant, maladaptive smooth muscle cell proliferation has prompted some investigators to liken restenosis to a neoplastic process (4,5). The term "malignant restenosis" has been used (6) to describe a syndrome characterized by rapid, refractory recurrences after repeated attempts at percutaneous coronary revascularization. When viewed from this perspective, the use of antimitogenic or antineoplastic agents is one of the most promising avenues of exploration in the search for a solution to the complex problem of restenosis.

Colchicine is an antimitogenic agent that binds to tubulin, disrupting spindle formation and resulting in the metaphase arrest of cell division. Colchicine has been shown to inhibit chemotaxis (7,8), collagen formation (9), muscle cell proliferation and platelet aggregation (10,11). In experimental animal models, this agent has prevented or reduced the formation of atherosclerotic plaques (12,13). Colchicine has also been effective in preventing myointimal proliferation after balloon arterial injury of the iliac artery in an atherosclerotic rabbit model (14) and has been reported to be effective in reducing fibroblastic proliferation in a patient with incipient hepatic cirrhosis (15). Colchicine has not been used previously in a clinical trial for the prevention of restenosis after coronary angioplasty.

From the Mid America Heart Institute, St. Luke's Hospital, Kansas City, Missouri. This study was presented in part at the 40th Annual Meeting of the American College of Cardiology, Atlanta, Georgia, March 1991.

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Methods

Study design. The study was designed as a double-blind randomized trial. The patients were randomized in a 2:1 fashion to treatment with oral colchicine, 0.6 mg twice daily, or placebo, one tablet twice daily. The 2:1 randomization scheme was used to maximize the number of patients treated with active drug and to encourage patient enrollment while preserving the statistical advantages of a randomized design. Treatment started within 24 h of angioplasty. Twenty-four percent of patients received one dose of colchicine or placebo before angioplasty; the remaining 76% of patients received their first dose within the 1st 24 h after angioplasty. Treatment was continued for 6 months or until the study end point (angiographic follow-up) was achieved.

Patients were scheduled for routine follow-up office visits at 3 and 6 months, at which time baseline laboratory studies were repeated. Laboratory work included a hematology profile; liver function tests, and measurements of serum creatinine, blood urea nitrogen, total cholesterol, triglycerides and high-(HDL) and low-(LDL) density lipoprotein levels. An exercise thallium stress test was performed at 3 months. Coronary arteriography was performed before angioplasty, immediately after angioplasty and at 6-month follow-up or earlier if the patient had recurrent angina or a markedly abnormal thallium stress test.

Selection of patients. Eligibility criteria for entry into the trial were 1) successful elective coronary angioplasty; 2) single or multivessel angioplasty; 3) bypass graft angioplasty; 4) angioplasty of previously undilated (new) and restenosed lesions; 5) angioplasty performed for silent ischemia and stable or unstable angina pectoris. Exclusion criteria were 1) direct angioplasty for acute myocardial infarction; 2) unsuccessful coronary angioplasty; 3) premenopausal women; 4) baseline leukopenia; 5) active peptic ulcer disease; 6) active diarrhea; 7) creatinine ≥2.5 mg/dl at baseline; 8) known colchicine intolerance. Successful angioplasty was defined as the reduction of the dilated lesion to ≤50% lumen diameter stenosis without documented acute reocclusion during the hospital stay. The research protocol was approved by the Institutional Review Board for Human Research at St. Luke's Hospital, Kansas City, Missouri. Informed consent was obtained from all patients before study enrollment.

Coronary angiographic measurements. The primary end point of the trial was angiographic restenosis. Angiographic measurements were made in a semiquantitative fashion by using an electronic caliper that was accurate to 0.01 mm. Lesion measurements, expressed as the minimal relative lumen diameter stenosis, were obtained by measuring each dilated lesion and adjacent angiographically normal segment three times in each of two orthogonal views. The relative lumen diameter stenosis was defined as the difference between the mean lumen diameter measurements of the normal segment and the dilated lesion divided by the mean lumen diameter of the normal segment. The measurements were taken on each lesion before angioplasty, immediately after angioplasty and at the 6-month follow-up study.

Table 1. Demographic Characteristics of Patients Treated With Colchicine or Placebo

	Colchicine (n = 130; 66%)	Placebo (n = 67; 34%)
Men	111 (85%)	58 (87%)
Mean age (yr)	59	62
Prior coronary bypass surgery	34 (26%)	17 (25%)
LVEF ≤40%	9 (7%)	5 (8%)
Class IV angina	52 (40%)	26 (39%)
Diabetes	16 (12%)	8 (12%)
Cholesterol (mg/dl)	213	208
Lesions dilated/pt	2.7	2.9

There were no significant differences between groups. Unless otherwise indicated all values indicate number of patients. Class IV = Canadian Cardiovascular Society functional class IV; LVEF = left ventricular ejection fraction; pt = patient.

Statistical analysis. The study protocol called for analysis of the angiographic data by two separate statistical methods. In one model, restenosis was evaluated as a continuous variable. In this noncategoric model, the stenosis measurements in each of the two groups were compared before angioplasty, immediately after angioplasty and at the time of the 6-month angiographic follow-up. The second method used the more traditional approach of analyzing restenosis as a dichotomous function. In this model, restenosis was defined as a return to ≥70% lumen diameter stenosis at the time of the follow-up study *and* a loss of ≥50% of the initial gain with angioplasty. When this definition was used, restenosis was evaluated categorically as a binary outcome for the presence or absence of restenosis.

Data were analyzed with chi-square analysis and a Student *t* test where appropriate. Statistical significance was defined as $p \leq 0.05$.

Results

Demographic data (Table 1). With the 2:1 randomization scheme, 130 patients (66% of the total group of 197 patients) were randomized to colchicine treatment and 67 patients (34%) to placebo treatment. The groups were very closely matched with respect to all major demographic characteristics. In the colchicine group, 2.7 lesions/patient were dilated; in the placebo group, 2.9.

Adverse effects (Table 2). Adverse drug effects occurred more frequently in colchicine- than in placebo-treated patients. Twenty-eight percent of colchicine-treated patients developed diarrhea that was often refractory and resulted in discontinuation of the drug in nine patients (7% dropout rate). Death occurred during the follow-up period in one colchicine-treated patient and in two placebo-treated patients (p = NS).

Angiographic follow-up. Complete angiographic follow-up was obtained in 145 of the 197 patients, yielding an

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Table 2. Adverse Drug Effects in 197 Patients Treated With Colchicine or Placebo

	Colchicine (n = 130)	Placebo (n = 67)
Diarrhea	36 (28%)	3 (5%)*
Nausea/vomiting	5 (4%)	4 (6%)
Rash	2 (1.5%)	1 (1.5%)
Dyspepsia	0	1 (1.5%)
Death	1 (0.8%)	2 (3%)
Dropout rate	9 (6.9%)	1 (1.5%)†

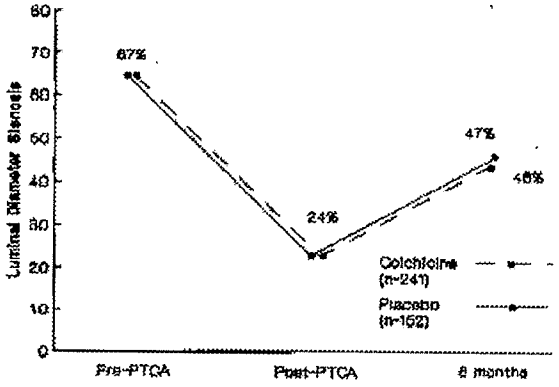
*p = 0.0001. †p = 0.15; other differences are not significant. Unless otherwise indicated, all values indicate number of patients.

angiographic follow-up rate of 74%. Follow-up coronary angiography was performed a mean of 5.5 months after angioplasty. Angiographic follow-up was not obtained in 52 patients because of death in 3 patients, dropout due to treatment side effects in 10 (9 receiving colchicine, 1 receiving placebo) and refusal to undergo elective follow-up catheterization in the remaining 39. In the 184 patients eligible for the 6-month cardiac catheterization (excluding patients who died or were intolerant to study medication), the follow-up rate was 79% (83% in placebo and 77% in colchicine groups, p = NS). In the 145 patients with complete angiographic follow-up, initial angiographic success was achieved in 393 (98%) of the 401 lesions dilated.

The restenosis rate was 22%/lesion in both the colchicine- and placebo-treated groups. Forty-one percent of colchicine-treated patients had restenosis in at least one lesion compared with 45% of the placebo-treated group (p = NS). The mean lumen diameter stenosis was essentially identical in the two groups at baseline, immediately after angioplasty and at 6-month follow-up (Fig. 1).

Thallium stress test data. A 3-month postangioplasty exercise thallium-201 stress test was performed in 118 (63%) of patients. Scintigraphic evidence for recurrent ischemia in the distribution of a dilated vessel was noted in 56 (58%) of 96 segments in the colchicine-treated patients and 27 (50%) of 54 segments in the placebo-treated patients (p = NS). Recurrent ischemia on thallium stress testing was noted in at least one dilated vessel distribution in 66% of the 73 colchicine-treated patients and in 58% of the 45 placebo-treated patients (p = NS).

Figure 1. The mean coronary lumen diameter stenoses of the placebo- and colchicine-treated groups were almost identical before angioplasty (Pre-PTCA), immediately after angioplasty (Post-PTCA) and at 6-month angiographic follow-up (p = NS). PTCA = percutaneous transluminal coronary angioplasty.



Discussion

Previous studies. In the current study, treatment with oral colchicine that was started at the time of coronary angioplasty had no effect on the subsequent rate of restenosis after angioplasty. In another trial (16) using colchicine preliminary results were also negative, although that trial used clinical nonangiographic end points. Although colchicine was demonstrated to be effective in reducing intimal proliferation after balloon injury to a rabbit iliac artery (14), the effect was apparent only with the highest dose of the medication. In that study, Currier et al. (14) found a reduced rate of restenosis in animals treated with high dose (0.2 mg/kg per day) but not with low dose (0.02 mg/kg per day) colchicine. In the standard 70-kg human, the high dose regimen would translate to 14 mg/day of colchicine. High dose colchicine has been used as an antineoplastic agent for conditions such as leukemia (5) but was poorly tolerated because of serious adverse effects, such as hemorrhagic gastritis and bone marrow suppression. Although the colchicine regimen in the current trial (1.2 mg/day) was considered to be relatively low dose, 7% of treated patients were unable to complete the study owing to severe gastrointestinal adverse effects (generally diarrhea). The incidence of significant diarrhea (28%) in the treated group in the current trial suggests that the systemic antimitogenic effects were adequate to interfere with gastrointestinal mucosal cell turnover. Furthermore, this same regimen (colchicine, 1.2 mg/day) was reported to be effective in reducing periportal fibrosis in the setting of incipient hepatic cirrhosis (15).

Limitations. The lack of consistent pretreatment in the current study is a potential limitation of the trial. However, the antimitogenic effects of colchicine are clinically apparent within hours of its use. Postmortem human studies (17) have shown that the migration of smooth muscle cells from the media to the intima occurs within the 1st 2 to 3 days after angioplasty. The actual proliferation of these cells begins shortly thereafter (11 to 30 days after angioplasty). Thus, antimitotic therapy with colchicine started at the time of the procedure should be adequate for the inhibition of subsequent myointimal proliferation.

Other neoplastic agents. Other neoplastic agents have been used in experimental animal angioplasty models. The hyperplastic smooth muscle cells responsible for the restenotic process are of mesenchymal cell origin (18). The chemotherapeutic agents generally used for tumors arising from mesenchymal cells include methotrexate, vincristine,

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cyclophosphamide and anthracycline antibiotic agents. Accordingly, the antineoplastic agents investigated so far in animals have generally been from this group of drugs. Combination therapy with vincristine and actinomycin D has been evaluated in a rabbit aortic model (19). Short-term therapy resulted in less smooth muscle cell hyperplasia 3 days after endothelial denudation in the rabbits treated with antineoplastic agents. The intermediate and long-term effects of this therapy were not observed in this study. The effectiveness of local methotrexate therapy on intimal proliferation after balloon arterial injury was evaluated by Muller et al. (20). After initial balloon arterial injury to the porcine carotid artery, methotrexate was intramurally administered through a Wolinsky coronary infusion balloon catheter (21). In this model, the local infusion of methotrexate did not abolish or even attenuate intimal proliferation. The use of systemic antineoplastic agents for restenosis was also addressed by Murphy et al. (22). In their trial utilizing a porcine coronary restenosis model, the use of oral or intramuscular methotrexate or azathioprine did not inhibit intimal proliferation and restenosis.

Clinical implications. The relatively low restenosis rate per lesion (22%) and per patient (43%) resulted from the use of a "conservative" definition of restenosis (as called for by the study protocol). The rate of restenosis per vessel by scintigraphic criteria on thallium-201 stress testing was significantly higher (55%). This finding suggests that some lesions had become hemodynamically significant again, although they had not returned to the baseline 70% lumen diameter stenosis, and had lost at least 50% of the initial gain with angioplasty. Additionally, many patients had more than one lesion dilated in a single vessel or vascular territory. Thus, they had an increased likelihood that recurrent ischemia would be detected in this distribution by tomographic thallium imaging, reflecting the additive risk of restenosis when multiple lesions are dilated (23).

Conclusions. The use of colchicine, although theoretically promising, proved ineffective in preventing restenosis after coronary angioplasty in the current study. Although the use of antineoplastic and antimitogenic agents in this application merits further consideration, therapy with higher doses and more potent agents will be limited to some degree by frequent, serious and even life-threatening adverse effects inherent in such regimens. Delivery systems to allow for local application of these agents may obviate some of these limitations.

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the less frequent use of atherectomy devices may provide an alternate explanation for the lower rate of postprocedural CABG. This seems unlikely since in our previous analyses,[10] device use was not associated with an increased frequency of CABG.

Coronary artery stents have been rapidly incorporated into clinical practice so that they are currently deployed in nearly 50% of all patients undergoing angioplasty procedures in a busy laboratory. A decline in the frequency of coronary bypass surgery for unsuccessful angioplasty is associated with this change in practice—a decline in the use of atherectomy devices, and no increase in length of stay for angioplasty patients.

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Lovastatin Plus Probucol for Prevention of Restenosis After Percutaneous Transluminal Coronary Angioplasty

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We hypothesized that combination therapy including lovastatin (for low-density lipoprotein [LDL] lowering) and probucol (for antioxidant activity) may be useful in reducing or preventing restenosis and recurrent coronary events after percutaneous transluminal coronary angioplasty (PTCA). The Angioplasty Plus Probucol/Lovastatin Evaluation (APPLE) trial was designed to test this hypothesis.

* * *

The APPLE trial was a randomized, double-blind, placebo-controlled study. The patients were randomized and started on therapy between 48 hours before and 24 hours after PTCA. Eligibility criteria included: (1) successful elective coronary PTCA (patients who underwent atherectomy, laser PTCA, or stent implantation were excluded); (2) age between 20 and 75 years; and (3) baseline total cholesterol values between 150 and 300 mg/dl. Exclusionary criteria were: (1) acute myocardial infarction; (2) failed PTCA; (3) abnormal baseline liver function tests; (4) secondary hypercholesterolemia (hypothyroidism, nephrotic syndrome, uncontrolled diabetes, and so forth); (5) previous sensitivity or intolerance to probucol or lovastatin; and (6) failure to give informed consent.

Patients were randomized in a 2:1 fashion to active therapy. Active therapy included lovastatin 20 mg twice daily and probucol 500 mg twice daily. Placebo patients received inactive placebo tablets that looked similar to the active medications (2 different pills twice daily). Therapy was continued for 6 months. Patients were seen for routine clinic visits at 3 and 6 months. Routine exercise treadmill testing was performed generally within the first 3 months after PTCA, and exercise thallium stress testing was performed variably at the managing physician's dis-

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TABLE I Demographics

Variables	Active (n = 142)	Placebo (n = 58)
Age (yr)	61 ± 9.7	62 ± 9.7
Sex		
Men	114 (80)	50 (86)
Women	28 (20)	8 (14)
Diabetic	16 (11)	11 (19)
Prior infarction	48 (34)	21 (36)
Prior coronary angioplasty	43 (30)	31 (53)
Angina Class III–IV	55 (39)	23 (40)
Total cholesterol (mg/dl)	211 ± 34	203 ± 30
High-density lipoprotein (mg/dl)	40 ± 13	39 ± 10
Low-density lipoprotein (mg/dl)	141 ± 30	136 ± 32
Triglycerides (mg/dl)	190 ± 204	192 ± 116

Values are expressed as mean ± SD or number (%).

TABLE II Follow-Up Lipid Profile (after 6 months of treatment)

Lipids	Active	Placebo
Cholesterol (mg/dl)	153 ± 33	216 ± 35*
High-density lipoprotein (mg/dl)	31 ± 12	42 ± 14*
Low-density lipoprotein (mg/dl)	98 ± 27	143 ± 34*
Triglycerides (mg/dl)	150 ± 86	197 ± 127
Total cholesterol/high-density lipoprotein (mg/dl)	4.93	5.12

*p < 0.05 active versus placebo.
Values are expressed as mean ± SD unless otherwise indicated.

TABLE III Angiographic Data (246 narrowings)

Percent Diameter Stenosis	Active (n = 142)	Placebo (n = 58)
Before angioplasty (%)	72 ± 14	66 ± 18
After angioplasty (%)	23 ± 17	19 ± 19
F/U stenosis (%)	50 ± 26	44 ± 28
Late loss (%)	26 ± 31	25 ± 31
Restenosis (% of patients)	51	46

p = NS for all variables.
Values are expressed as mean ± SD unless otherwise indicated.
F/U = follow-up.

cretion within the first 6 months. Fasting serum lipids, liver function tests, and creatine phosphokinase levels were measured at baseline and at 6 months. Resting electrocardiograms were obtained at baseline, hospital discharge, and again at 6 months. Cardiac catheterization was performed at 6 months if any clinical abnormalities to suggest significant recurrent coronary artery disease were noted either subjectively (patient complaints) or objectively (stress testing, resting electrocardiograms, and so forth). At the end of 6 months, the patients were unblinded. The primary end point of the study was defined as the change in quantitative angiographic luminal diameter stenosis in the dilated segments between the immediate post-PTCA results and the 6-month follow-up angiograms. Secondary end points were: (1) 50% luminal diameter stenosis by quantitative analysis on the follow-up angiogram; and (2) clinical cardiac events including repeat coronary PTCA, bypass graft surgery, myocardial infarction, or death. A Student's *t* test was utilized for comparing continuous variables and Fisher's exact test for categorical variables. Analysis of variance was utilized for evaluating changes in lipid levels and quantitative angiographic changes during the study. Angiographic data were compared using an "efficacy analysis" rather than "intention to treat analysis."

A total of 239 patients were enrolled; 163 (68%) were randomized to active therapy, and 76 (32%) to placebo. During the course of the trial, 39 patients were withdrawn from the study including 21 (13%) in the active arm and 18 (24%) in the placebo arm. Most of these patients were withdrawn due to noncompliance with requirements for study participation. Most of these patients discontinued study medications without citing a specific

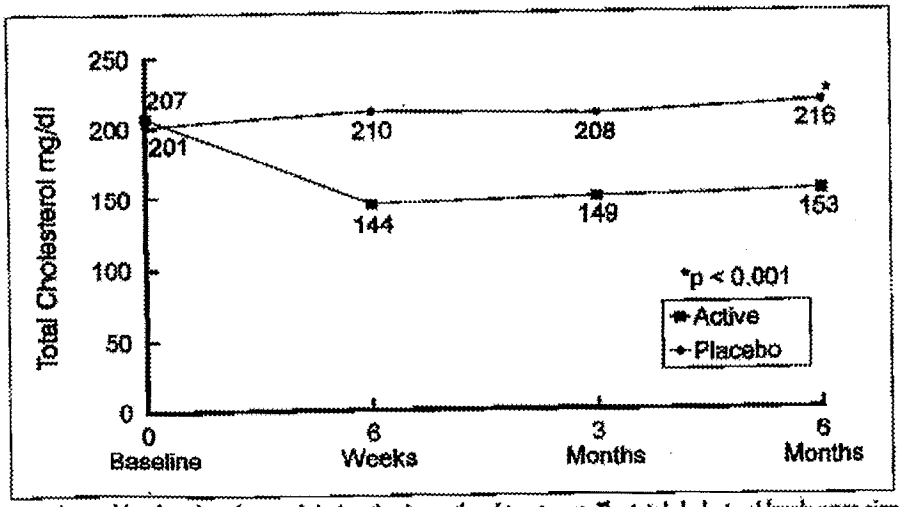

FIGURE 1. Total cholesterol levels at baseline and during the 6 months of treatment. The total cholesterol levels were significantly reduced in the group of patients taking active therapy compared with those receiving placebo.

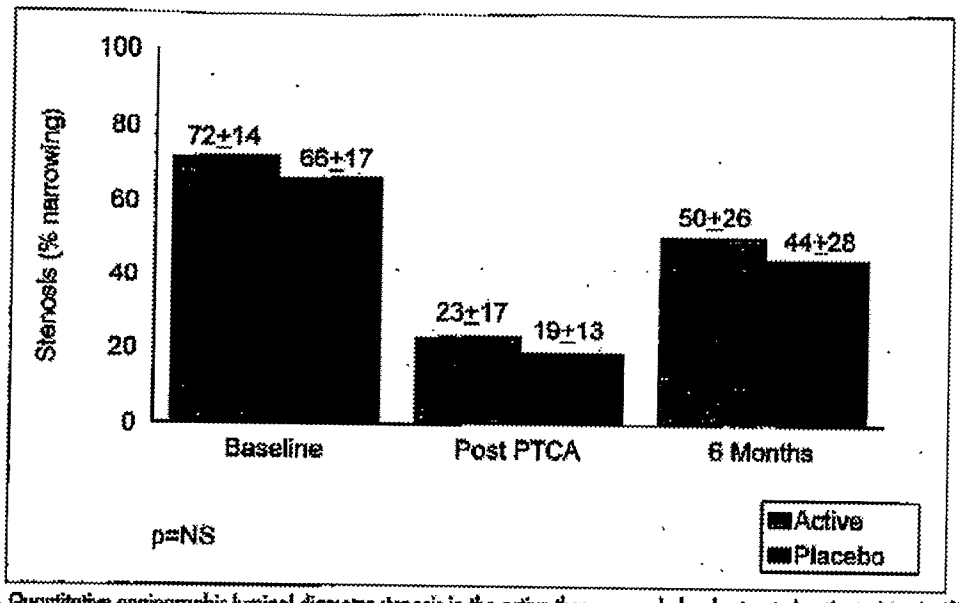

FIGURE 2. Quantitative angiographic luminal diameter stenosis in the active therapy- and placebo-treated patients. No significant differences were noted between the 2 groups (p = NS) either at baseline, immediately after percutaneous transluminal coronary angioplasty (Post PTCA), or at 6-month follow-up angiogram.

reason and the incidence of adverse events was similar in the 2 groups.

The demographics of the active and placebo groups were statistically similar (Table I). The sites of the dilated lesions were left anterior descending in 37%, left circumflex in 25%, right coronary system in 32%, and a bypass graft in 10%. The distributions of index lesion location were similar in the active treatment and placebo groups. The lipid levels remained essentially unchanged throughout the study period in the placebo group, while the mean total cholesterol level decreased 27%, LDL decreased 30%, and high-density lipoprotein (HDL) decreased 27% in the active therapy group. The total cholesterol to HDL ratio did not change in the active therapy group due to the significant and proportional decreases in both total cholesterol and HDL levels during treatment with lovastatin and probucol. At the end of the study, the total cholesterol/HDL ratios were similar in both active and placebo groups. Details of the changes in the lipid parameters are outlined in Table II and Figure 1.

In the group of patients taking active therapy, a mean of 2.2 ± 1.7 narrowings were dilated per patient compared with 1.9 ± 1.1 narrowings per patient in the placebo group (p = NS). Angiographic restudy was performed in 82 of the 142 patients in the active therapy group (58%) versus 35 of the 58 placebo patients (60%, p = NS). Because study funding was not available for follow-up angiography, the restudy rate was relatively low. The complete quantitative angiographic data for the 180 dilated lesions in the active therapy group and the 66 dilated lesions in the placebo group are depicted in Table III and Figure 2. There were no significant differences between the active and placebo groups with respect to restenosis by quantitative angiography. A total of 51% of the patients in the active group were noted to have a minimal luminal diameter of ≥50% at ≥1 of the dilated sites compared with 46% of the pla-

TABLE IV Events Within Six Months

	Active (n = 142)	Placebo (n = 58)
Repeat coronary angioplasty	50 (35)	22 (38)
Bypass surgery	7 (5)	3 (5)
Death	1 (1)	1 (2)
Myocardial infarction	3 (2)	1 (2)
Any event	53 (37)	24 (41)

p = NS for all variables.
Values are expressed as number (%).

TABLE V Adverse Events

	Active (n = 163)	Placebo (n = 76)
Gastrointestinal upset	4 (2.5)	2 (2.6)
Myalgias	2 (1.2)	0
Elevated creatine phosphokinase	2 (1.2)	0
Elevated hepatic enzymes	5 (3)	1 (1.3)
Rash	1 (0.6)	2 (2.6)
Death	1 (0.6)	1 (1.3)
Prolonged QT	2 (1.2)	0
Depression	1 (0.6)	0
Ulcer	2 (1.2)	1 (1.3)
Constipation	0	1 (1.3)
Nonspecific	1 (0.6)	1 (1.3)

p = NS for all variables.
Values are expressed as number (%).

cebo-treated patients (p = NS). Recurrent cardiac events during the study were also similar in the 2 groups (Table IV).

A single death occurred in each of the groups during the 6-month follow-up period. Neither of these deaths were believed to be related to the study medication. A reversible defect (ischemia) was noted in the distribution of ≥1 of the dilated vessels on 6-month post-PTCA tomographic thallium stress testing in 45 of 85 patients (53%) receiving active therapy and in 17 of 37 placebo patients (46%) (p = NS). Elevated creatine phosphokinase levels were noted in 1.2% of the patients in the active group and in no patient in the placebo group. Elevated liver enzymes were noted in 3% of patients in the active therapy group and in 1.3% of the patients in the placebo group. The adverse events are outlined in Table V.

* * *

This randomized trial using lovastatin to lower LDL levels and probucol to prevent LDL oxidation documented this combination therapy to be ineffective in preventing restenosis or recurrent cardiac events, or both, throughout the first 6 months after PTCA. The combination of lovastatin and probucol was highly effective at reducing total cholesterol (−27%) and LDL (−30%) levels; unfortunately, the HDL levels were also proportionately reduced (−27%), leaving the total cholesterol to HDL ratio unchanged in the active treatment group compared with the placebo group. Similar findings with respect to HDL levels have been reported in previous studies that have utilized probucol.[1] HDL cholesterol has been repeatedly shown to have profound antiatherosclerotic effects and many recent studies have shown that the HDL level or the total cholesterol to HDL ratio, or both, are among the most important determinants of risk for progressive atherosclerosis.[2] It is possible that the counterproductive HDL-lowering effects of probucol mitigated some of the inherent antiatherosclerotic potential of this powerful antioxidant compound. Probucol previously had not been tested in a trial designed to prevent restenosis, but was found to be ineffective in preventing progressive femoral artery atherosclerosis in a 5-year randomized prospective study recently published.[1] Studies using monotherapy with lovastatin for preventing restenosis have shown divergent results.[3–5] However, the large prospective Lovastatin Restenosis Trial (LRT) was negative.[6,7]

The combination of moderate-dose lovastatin and full-dose probucol was found to be safe and well tolerated in this study. Transient elevation of the liver enzyme levels occurred in 5 of the 163 patients (3%) taking active therapy in the study. Abnormal muscle enzyme levels, myalgias, and significant prolongation of the QT interval were rare in patients taking active therapy and not statistically more common than in the placebo group. Adverse effects necessitating withdrawal from study medication were not more common in the group receiving lovastatin and probucol than in the placebo group.

In summary, combination lovastatin and probucol effectively reduced lipid levels but did not prevent restenosis or clinical events during the first 6 months.

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Quinapril Prevents Restenosis After Coronary Stenting in Patients With Angiotensin-Converting Enzyme D Allele

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Restenosis after coronary artery stent implantation is attributed chiefly to intimal hyperplasia, which is prevented experimentally by angiotensin-converting enzyme (ACE) inhibitors. Therefore, the present study investigated whether the effect of quinapril, a tissue-specific ACE inhibitor, on the prevention of coronary restenosis differs according to ACE polymorphism. One hundred consecutive patients with successful stent implantation were randomly assigned to quinapril and control groups. Both follow-up angiography and ACE polymorphism analysis were obtained from 92 patients (control, 46; quinapril treatment, 46). The prevalence of risk factors did not differ statistically according to quinapril treatment or ACE genotypes. There was no statistically significant difference in the occurrence of restenosis 6 months after stenting between the groups. Quantitative coronary angiography revealed that quinapril treatment resulted in significantly higher minimal lumen diameter and significantly lower percent diameter stenosis (22.9±22.6 vs 37.1±19.7% in the control group, $p<0.05$) in patients with the D allele although there was no difference in those with the II genotype. In addition, intravascular ultrasound revealed that quinapril treatment significantly prevented the loss of minimal lumen cross-sectional area and the increase in percent area stenosis (34.5±14.0 vs 53.3±16.4% in the control group, $p<0.05$) in patients with the D allele compared to those with the II genotype. These results suggest that the administration of ACE inhibitors for the attenuation of lumen loss after coronary stent implantation is best for subjects with the D allele of the ACE genotype. (*Circ J* 2002; **66**: 311–316)

Key Words: Angiotensin-converting enzyme; Polymorphism; Quinapril; Restenosis; Stent

Although coronary angioplasty has become an established treatment for patients with occlusive coronary artery disease, the prediction and prevention of restenosis after the intervention, regardless of the technique, remains an important unresolved issue[1,2] The balloon expandable stent was developed to improve the short- and long-term results of coronary angioplasty, and its application markedly improved acute outcome, but the later loss of lumen area persists as a significant limitation of intracoronary stent placement[3–5] However, little is known about the molecular mechanisms of restenosis after coronary angioplasty with or without stent implantation. A number of studies have attempted to elucidate its mechanism and prevent restenosis, using both patients and animal models, respectively[6,7]

Angiotensin-converting enzyme (ACE) may play an important role in restenosis after coronary angioplasty through the proliferation of vascular smooth muscle cells by production of angiotensin II and inhibition of bradykinin[8] However, randomized trials with ACE inhibitors, such as cilazapril[9,10] and fosinopril[11] have failed to inhibit the occurrence of angiographic restenosis after coronary balloon angioplasty. The mechanism by which restenosis occurs after coronary artery intervention may differ between conventional balloon angioplasty and intracoronary stent implantation[12] In-stent restenosis results predominantly from neointimal hyperplasia consisting of smooth muscle cell migration and extracellular matrix formation[6] not from late recoil. The present study was designed to evaluate the relationship between the effect of quinapril, a tissue-specific ACE inhibitor with high affinity[13] and an insertion/deletion (I/D) polymorphism of the ACE gene on the prevention of restenosis after coronary stent implantation[14] We present our data from quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) carried out in patients who underwent successful coronary stent implantation.

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Methods

Study Population

The study population consisted of 100 consecutive patients who underwent successful implantation of a Palmaz-Schatz stent in Ogaki Municipal Hospital. The aim of the coronary stenting was an 'optimal' result after elective balloon angioplasty for an angiographically proven, functionally significant narrowing in major coronary arteries. All of the patients were prospectively asked to undergo a systematic 6-month angiographic follow-up. Patients were randomly assigned to the quinapril treatment group (10 mg or 20 mg of quinapril daily (average dose of 18 mg/day) from the day after stenting) or the control group

after stent implantation. No placebo tablets were administered in the control group. There was no protocol regarding calcium antagonists, nitrates or β-blockers. The aims of the study were explained to each patient and informed consent was obtained. The trial was carried out according to the Declaration of Helsinki.

Angioplasty and Stenting Procedures

Treatment with 200 mg ticlopidine and 81 mg aspirin was administered daily before the procedure and continued until the time of follow-up. Balloon dilatation was performed according to the conventional technique. A Palmaz-Schatz stent with delivery sheath developed at nominal pressures was used; each stent was then expanded with a noncompliant balloon of the same diameter as the reference vessel segment, with inflation in the range of 14–16 atm for 30–60 s.

Angiographic Assessment and QCA

A coronary arteriogram was obtained before balloon angioplasty, after stent replacement, and at follow-up after the administration of 0.2 mg intracoronary nitroglycerin. QCA was performed independently by 2 core angiographic laboratories blinded to the treatment assignment. Reference lumen diameter and minimal lumen diameter were determined by a computer-assisted, edge-detection algorithm using an offline system (QCA-CMS System, MEDIS Inc). Follow-up angiography was performed in the same projections as those used in the baseline study. Using the outer diameter of the contrast-filled catheter as the calibration, the minimal lumen diameter in diastole from the 'worst' view was recorded. The reference was averaged from 10-mm-long angiographically normal segments proximal and distal to the lesion; when a normal proximal segment could not be identified (eg, ostial lesion location), only a distal segment was analyzed. The percent diameter stenosis was calculated from the minimal lumen diameter and the reference. To define restenosis, we used a categorical approach with the criterion of ≥50% diameter narrowing within the stent and in the segment, including the stent plus its edges (within 5 mm) at follow-up.

IVUS Measurements

The IVUS system (Cardiovascular Imaging Systems, Inc, Boston, MA, USA) incorporated a 30-MHz beveled transducer mounted on the end of a flexible shaft that rotates at 1,800 rpm within a 3.2F imaging sheath (Ultra Cross TM 3.2; Boston Scientific SCIMED, Natick, MA, USA). All studies were recorded during transducer pullback on a high resolution super-VHS tape for off-line analysis at a pullback speed of 0.5 mm/s. The cross-sectional area of intimal hyperplasia present within the stent was calculated as the stent cross-sectional area minus the lumen cross-sectional area. The reference lumen cross-sectional areas were the lumen areas at the most visually normal anatomic cross sections within 10 mm proximal and distal to the stent but before any major side branches. When a stent was ostial in location, only the distal reference lumen was measured.

DNA Analysis for the Detection of ACE Genotype

ACE polymorphism was obtained in 92 of the 99 patients analyzed in our initial study[14] In that study there were 46 subjects in the control and quinapril groups each. The quinapril and control groups were then divided into 2 subgroups: patients with the D allele (DD and ID genotype) and patients without (II genotype). Samples of venous blood for DNA analysis were collected after follow-up coronary angiography. Leukocytes were isolated from blood samples containing ethylene diamine tetraacetic acid (EDTA) disodium using Ficoll-Hypaque solution (Pharmacia, Uppsala, Sweden)[15] DNA was extracted from the lymphocytes with the use of a QIAamp Blood Kit (QIAGEN Inc, Chatsworth, CA, USA). The I/D polymorphism of the ACE gene was determined in the presence of 5% dimethysulfoxide to enhance amplification of the ACE I allele according to a method previously described[16] Reaction products were loaded onto a 2.0% agarose gel and electrophoresed, then the gel was treated with ethidium bromide. DNA fragments were confirmed by comparison with known size markers.

Baseline Data Collection

A history of smoking was obtained during subject interviews. The subjects with a history of taking medication for hypertension or those whose average blood pressure was ≥90 mmHg in diastole and/or ≥140 mmHg in systole by 2 or more measurements were labeled as hypertensive. Diabetes mellitus was diagnosed by the 1997 criteria of the American Diabetes Association. The body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Fasting blood samples were collected for plasma lipid concentrations. Plasma levels of total cholesterol and those of triglycerides were measured by enzymatic methods. The plasma level of high-density lipoprotein (HDL) cholesterol was determined with enzymatic reagents after precipitating the apolipoprotein B-containing lipoproteins with heparin, Ca^{2+}, and Ni^{2+}. The concentration of low-density lipoprotein (LDL) cholesterol was calculated with the formula described by Friedewald et al[17]

Statistical Analysis

The results are shown as mean ± SD. Data were collected and stored in an Apple computer (Apple Japan Inc, Tokyo, Japan) using Statview 5.0 software (SAS Institute Inc, Cary, NC, USA). One-way analysis of variance (ANOVA) followed by the Student-Newman-Keuls multiple-range test as a post hoc test, or by the chi-square test, as appropriate, was used to compare the differences between 2 groups. A level of $p<0.05$ was considered significant.

Results

Follow-up angiography and ACE polymorphism analysis were obtained from 92 patients: 46 in the control group and 46 in the quinapril treatment group. There were no significant differences between the control and quinapril treatment groups with regard to lesion characteristics such as location or lesion type (Table I).

Results of the ACE I/D polymorphism revealed that there were 23 subjects with genotype II, 8 with ID, and 15 with DD in the control group, and 26 with II, 14 with ID, and 6 with DD in the quinapril treatment group, indicating that there was no significant difference in the distribution of ACE genotype between the 2 groups. Given that the number of subjects enrolled in the present study was small, and that the D allele dominant effect was more prominent than its recessive effect in the results, the subjects were divided into 2 subgroups, those with the D allele (ID+DD group) and those without (II group).

The 4 groups divided according to treatment and genotype were well matched for age and sex. The prevalence of

Table 1 Baseline Angiographic Characteristics

	Control group (n=46)	Quinapril group (n=46)	p value
Lesion location			
Left anterior descending	25	27	
Left circumflex	5	8	
Right coronary artery	16	11	0.43
ACC/AHA lesion type			
A	5	6	
B1	17	15	
B2	13	12	
C	10	13	0.89
Moderate or severe calcification	7	4	0.34
Eccentric lesion	23	22	0.83
Ostial Lesion	2	4	0.40

Table 2 Clinical and Biochemical Characteristics Assigned to ACE Inhibitor Therapy and ACE Genotype

	Control group		Quinapril group	
	II (n=23)	ID+DD (n=23)	II (n=26)	ID+DD (n=20)
Age (years)	62.8±7.8	63.5±9.3	66.0±9.8	65.0±9.0
Gender (M/F), n	19/4	18/5	20/6	16/4
Body mass index (kg/m²)	23.8±3.4	24.6±2.7	23.4±2.6	23.7±2.6
Smoking history, n (%)	6 (26)	6 (26)	6 (23)	10 (50)
Hypertension, n (%)	8 (35)	5 (22)	11 (42)	5 (25)
Diabetes mellitus, n (%)	4 (17)	7 (30)	7 (27)	5 (25)
Total cholesterol (mmol/L)	5.49±1.06	4.87±0.67	5.04±0.77	4.56±0.81
LDL cholesterol (mmol/L)	3.23±0.92	3.04±0.53	3.29±0.78	2.69±0.77
HDL cholesterol (mmol/L)	1.28±0.38	1.19±0.26	1.12±0.36	1.09±0.31
Triglycerides (mmol/L)	1.87±0.80	1.42±0.65	1.57±0.90	1.45±0.95

Results are given as mean±SD. There were no significant differences among the groups by ANOVA or chi-square test.

Table 3 Quantitative Coronary Angiographic Results Assigned to ACE Inhibitor Therapy and ACE Genotype

	Control group		Quinapril group	
	II (n=23)	ID+DD (n=23)	II (n=26)	ID+DD (n=20)
Restenosis, n (%)	6 (26)	5 (22)	4 (15)	1 (5)
Reference (mm)				
Before intervention	3.01±0.48	2.97±0.50	2.94±0.46	3.32±0.63
After intervention	2.98±0.48	3.00±0.30	3.01±0.41	3.25±0.77
Follow-up	2.93±0.52	3.07±0.38	2.95±0.40	3.13±0.64
MLD (mm)				
Before intervention	0.61±0.29	0.58±0.53	0.56±0.31	0.72±0.41
After intervention	3.26±0.46	3.27±0.50	3.31±0.44	3.31±0.56
Follow-up	1.87±0.81	1.95±0.58	1.91±0.75	2.33±0.86*†
Diameter stenosis (%)				
Before intervention	79.9±10.1	81.9±15.9	81.0±11.1	78.4±12.1
After intervention	−10.1±10.0	−9.0±13.3	−10.7±13.7	−3.3±10.7
Follow-up	37.2±22.5	37.1±19.7	36.4±22.6	22.9±22.6*†

*Results are given as mean±SD. MLD, minimal lumen diameter. *p<0.05 compared with II genotype in the quinapril group. †p<0.05 compared with ID+DD genotypes in control group. Statistics were performed by ANOVA followed by the Student–Newman-Keul multiple-range test.*

risk factors such as BMI, smoking habit, hypertension, and diabetes did not differ statistically among the groups (Table 2). Likewise, there were no significant differences in plasma lipid concentrations among the groups, although total cholesterol and LDL cholesterol concentrations showed a tendency toward lower levels in the ID+DD subgroup of both the control and quinapril treatment groups.

Follow-up coronary angiography was performed at 6 months after stent implantation and the angiographic characteristics by QCA analysis are shown in Table 3. Restenosis in the ID+DD group of the quinapril treatment group was observed in only 1 patient, though there was no statistically significant difference in the occurrence of restenosis among the groups (p=0.29). QCA analysis showed no differences in the reference diameter among the groups before intervention, after intervention, or at follow-up angiography. With regard to minimal lumen diameter of stents at follow-up angiography, a significantly higher dimension was obtained in the ID+DD group of the quinapril treatment group as compared with that in the ID+DD group of the control or the II group of the quinapril treatment group (2.33±0.86 mm vs 1.95±0.58 mm or 1.91±0.75 mm, respec-

Table 4 Quantitative Planar Intravascular Ultrasound Analysis Results Assigned to ACE Inhibitor Therapy and ACE Genotype

	Control group		Quinapril group	
	II (n=16)	ID+DD (n=15)	II (n=19)	ID+DD (n=9)
Reference lumen cross-sectional area (mm²)				
After intervention	8.6±2.3	7.8±1.6	7.1±1.5	9.6±3.0†
Follow-up	7.5±2.1	7.5±1.9	7.1±1.6	8.0±2.2
Minimal lumen cross-sectional area (mm²)				
After intervention	7.4±1.4	7.0±1.4	6.7±1.5	8.0±2.0
Follow-up	4.1±1.5	3.3±1.1	4.1±1.1	5.2±1.1**†
Area stenosis (%)				
After intervention	13.9±16.2	6.9±17.7	4.9±22.4	14.7±16.0
Follow-up	46.2±16.1	53.3±16.4	41.0±16.6	34.5±14.0*

Results are given as mean±SD. *p<0.05 and **p<0.01 compared with ID+DD genotypes in control group. †p<0.05 compared with II genotype in the quinapril group. Statistics were performed by ANOVA followed by the Student–Newman-Keul multiple-range test.

tively; p<0.05), despite a lack of difference in minimal lumen diameter before and after intervention. On the other hand, the percent diameter stenosis at angiographic follow-up was significantly lower in the ID+DD group of the quinapril treatment group than that in the ID+DD group in the control or in the II group of the quinapril treatment group (22.9±22.6 vs 37.1±19.7 or 36.4±22.6%, respectively; p<0.05). When the subjects were not divided according to the genotype, the preventive effect of quinapril treatment was not observed.

In a small number of patients, we assessed in-stent restenosis using IVUS (Table 4). IVUS analysis also revealed that quinapril treatment of patients with the D allele prevented the loss of minimal lumen cross-sectional area (5.2±1.1 vs 3.3±1.1 mm² in the control patients with the D allele, p<0.01) and attenuated the increase in percent area stenosis calculated from the stent cross-sectional areas (34.5±14.0 vs 53.3±16.4% in the control patients with the D allele, p<0.05).

Discussion

We recently reported on the effect of quinapril on in-stent restenosis in 99 patients who underwent successful coronary angioplasty and stent implantation.[14] In our study, based on IVUS analysis, quinapril treatment attenuated the decrease in minimal luminal area and lumen volume at 6 months in stented coronary artery segments. However, angiographic analysis failed to demonstrate a significant difference in minimal luminal diameter between the quinapril and control groups at 6 months. Quinapril has high tissue specificity for ACE, and the dissociation of the drug from the enzyme is markedly prolonged.[13] ACE inhibition with quinapril treatment can ameliorate endothelial dysfunction, which may be one of the first steps in the development of atherosclerosis,[8] in patients with coronary artery disease.[9] The present study shows that the ACE inhibitor, quinapril, has a potential protective effect on late luminal narrowing after successful coronary artery stent implantation, and that susceptibility to the favorable effect on diminishing loss of lumen diameter is associated with ACE I/D polymorphism. Our data indicate that administration of the ACE inhibitor may be effective only in patients with the D allele.

Our study had some limitations. It was not double blind and additionally, a placebo tablet was not given to the control group. Lastly, the total and LDL cholesterol levels were lower in the patients with the D allele compared with patients without the D allele.

The renin–angiotensin system has been implicated in the pathogenesis of neointimal hyperplasia.[20] The I/D polymorphism in the ACE gene is associated with marked differences in serum[21] and cellular ACE levels.[22] Namely, individuals with the ACE D allele show higher levels of blood and cellular ACE concentrations. Although a recent report showed a slight association between ACE I/D polymorphism and the level of blood pressure in Japanese subjects,[23] most previous studies have reported no association.[24] Regarding ischemic heart disease, an up to date large-scale study discussing the association between myocardial infarction and the D allele, concluded that a weak relationship exists between the two (risk ratio 1.10, 95% confidence interval 1.00–1.21).[25] In addition, no influence of ACE polymorphism on restenosis after coronary angioplasty[26] or stent implantation[27] were reported, which is consistent with our results in the control group.

Evidence that ACE inhibitors effectively limit restenosis has been reported in animal models,[20,28,29] but has proven ineffective for restenosis in humans after coronary balloon angioplasty in multicenter, double-blind, placebo-controlled trials.[9–11] On the basis of the findings from animal models, restenosis was initially considered to occur because of neointimal hyperplasia in response to endothelial injury.[20] In contrast, intracoronary ultrasound studies in humans suggest that chronic remodeling rather than neointimal hyperplasia is the major mechanism of restenosis after conventional coronary balloon angioplasty.[30] On the other hand, the stent prevents the remodeling process as well as the elastic vessel recoil and plaque persistence; therefore, restenosis after coronary stenting is chiefly a consequence of neointimal hyperplasia in conjunction with the stent.[12] Thus, ACE inhibitors, which have been experimentally proven to have protective effects against neointimal hyperplasia, are more likely to prevent restenosis after stent implantation as compared with conventional balloon angioplasty. The results demonstrated here show that, on the basis of the findings shown in percent diameter stenosis by QCA analysis and percent area stenosis by IVUS analysis, quinapril treatment had no effect on the prevention of restenosis in the patients with the II genotype.

The result that only subjects with the D allele benefited from the preventive effect on restenosis by quinapril treatment could be attributed to higher levels of ACE activity in these subjects than in those with the II genotype. The subjects with the higher levels of ACE activity are considered to respond to ACE inhibitor treatment with a greater decrease in ACE activity. Amant et al have reported that

the D allele of the ACE gene is associated with greater late luminal loss after intracoronary stent implantation, most likely by higher levels of plasma ACE[31] Our results do not conflict with their expectations. In fact, studies in patients with nephropathy showed that the improvement of proteinuria was greater in subjects with the D allele than in those with the II genotype[32,33] Recently, Prasad et al have reported that ACE inhibitor treatment results in a greater improvement of endothelial dysfunction in subjects with the D allele[34] We expect that the II genotype patients with coronary artery stenosis have more risk factors than those with the D allele because the former group suffer from coronary heart disease even in the absence of the D allele. It should be noted that the levels of total plasma and LDL cholesterol in the subjects with the II genotype were higher than those in subjects with the D allele. It has been claimed that the protective effect on restenosis in subjects with the D allele is from the lower levels of LDL cholesterol in the ID+DD. In light of our finding that patients with the II genotype did not have a beneficial effect of the quinapril treatment, this favorable effect on restenosis was achieved by inhibition of the renin-angiotensin system. Given that multiple factors are associated with the development of neointimal hyperplasia[6] sufficient protection from restenosis could not be obtained by the administration of an ACE inhibitor only.

To our knowledge, the PARIS Study by Meurice et al is the only other published study on the effect of quinapril on in-stent restenosis[35] Even though they reported a prostenotic effect with quinapril compared with placebo in patients with the DD ACE genotype, their study is not similar to our study. Most importantly, the ethnic backgrounds of the patients are different. Because the sample sizes are small, the PARIS Study and ours are only pilot studies and further studies are required before a definitive conclusion can be made on the effect, if any, of quinapril on coronary artery in-stent restenosis.

Our results suggest that the administration of ACE inhibitors for the attenuation of the lumen loss after coronary stent implantation is more beneficial in subjects with the D allele of the ACE genotype. In other words, treatment with an ACE inhibitor is not expected to result in inhibition of neointimal hyperplasia in subjects with the II genotype. The determination of the ACE genotype in patients will enable selective treatment for patients after coronary artery intervention.

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LONG-TERM TREATMENT WITH A PLATELET GLYCOPROTEIN-RECEPTOR ANTAGONIST AFTER PERCUTANEOUS CORONARY REVASCULARIZATION

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ABSTRACT

Background When administered intravenously at the time of percutaneous coronary revascularization, glycoprotein IIb/IIIa receptor antagonists decrease the incidence of death and nonfatal myocardial infarction and the need for urgent revascularization. We hypothesized that long-term administration of oral glycoprotein IIb/IIIa antagonists, which block the aggregation of platelets, might stabilize intravascular plaque and prevent additional ischemic cardiac events.

Methods We conducted a prospective, double-blind trial in which 7232 patients were randomly assigned to receive 20 mg of oral xemilofiban or placebo 30 to 90 minutes before undergoing percutaneous coronary revascularization, with maintenance doses of 10 or 20 mg of xemilofiban or placebo administered three times daily for up to 182 days. There were two primary composite end points: one was death, nonfatal myocardial infarction, or urgent revascularization at 182 days, and the other was death or nonfatal myocardial infarction at 182 days.

Results Death, myocardial infarction, or urgent revascularization occurred within 182 days in 324 patients who received placebo (Kaplan–Meier cumulative event rate, 13.5 percent), 332 who received 10 mg of xemilofiban (13.9 percent, $P=0.82$ for the comparison with placebo), and 308 who received 20 mg of xemilofiban (12.7 percent, $P=0.36$ for the comparison with placebo). The incidence of death or myocardial infarction was also similar in all three groups. Clinically significant hemorrhagic complications and thrombocytopenia were infrequent.

Conclusions The administration of the glycoprotein IIb/IIIa antagonist xemilofiban before percutaneous coronary revascularization and for up to six months thereafter does not significantly reduce the incidence of important clinical end points. (N Engl J Med 2000;342:1316-24.)

THE activation and aggregation of platelets are thought to be responsible for the development of thrombi that lead to ischemic events after percutaneous transluminal coronary revascularization (PTCR).[1] The aggregation of platelets is mediated by the binding of fibrinogen to the platelet glycoprotein IIb/IIIa receptor.[2,3] Numerous trials have demonstrated that the administration of intravenous glycoprotein IIb/IIIa receptor antagonists immediately before and during the 24- to-48-hour period after PTCR reduces the incidence of death and myocardial infarction and the need for urgent revascularization.[4-15] The reduction in ischemic events persisted for 30 days or more in some studies, but the benefit was derived from a reduction in early ischemic events rather than from continued prevention of new events. Since platelet activation persists for up to 1 month after the onset of acute coronary syndromes[16] and since reocclusion may occur for up to 21 days after the implantation of a stent,[17] long-term oral treatment with a glycoprotein-receptor antagonist may have clinical value.

Current oral antithrombotic regimens for PTCR have serious limitations. Although ticlopidine has been widely used with aspirin to prevent thrombosis after stent placement, the Food and Drug Administration has not approved the use of the drug for this indication.[18-26] In addition, ticlopidine causes neutropenia and thrombotic thrombocytopenic purpura,[27,28] and restenosis within the stent remains a problem.[29-32]

The Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial tested the hypothesis that long-term oral administration of a glycoprotein IIb/IIIa receptor antagonist would provide sustained protection from death, myocardial infarction, and the need for urgent revascularization.

METHODS

Study Design

Our phase 3 trial was a double-blind, randomized, placebo-controlled study conducted at 412 centers in North and South America, Europe, Israel, Australia, New Zealand, and South Africa. The protocol for the trial has been described in detail elsewhere.[33]

Enrollment of Patients

Patients with angiographic evidence of clinically significant coronary artery disease necessitating PTCR were eligible for the study. Patients at high risk for ischemic events[34] were sought in order to maximize the event rate and thus increase the opportunity to

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*The investigators who participated in the Evaluation of Oral Xemilofiban in Controlling Thrombotic Events (EXCITE) trial are listed in the Appendix.

demonstrate a therapeutic effect. Patients who had received abciximab before PTCR were not eligible for enrollment.

The main exclusion criteria were a history of bleeding disorders or active bleeding, thrombocytopenia (platelet count, <120,000 per cubic millimeter), coagulation-factor deficiency, uncontrolled hypertension, major trauma or surgery within the previous three months, thrombolytic treatment within six hours before revascularization, a serum creatinine level higher than 1.5 mg per deciliter (132.6 μmol per liter), an inability to discontinue oral anticoagulant therapy, nonhemorrhagic stroke within the previous two months, a history of hemorrhagic stroke, or an inability to provide informed consent.

Study Protocol

We tested the efficacy of xemilofiban administered orally in a dose of 10 or 20 mg given three times daily for up to six months. These doses were selected to minimize the risk of excessive bleeding during the treatment period. The level of inhibition of adenosine diphosphate–induced platelet aggregation is 40 to 70 percent with the 10-mg regimen and 60 to 90 percent with the 20-mg regimen.[35] The protocol was approved by the institutional review board of each participating hospital, and all patients gave written informed consent before they were enrolled in the study.

After the diagnostic angiogram had been obtained and before PTCR was performed, patients were randomly assigned to one of three regimens: a single oral dose of 20 mg of xemilofiban administered before PTCR and a maintenance dose of 20 mg given three times daily after the procedure, a single oral dose of 20 mg of xemilofiban administered before the procedure and a maintenance dose of 10 mg given three times daily, or placebo administered both before and after the procedure. The random assignments were made by telephone with the use of an interactive voice-response computer system and were stratified according to the study center. Among patients in whom stents were implanted, those in the placebo group also received ticlopidine, in a dose of 250 mg administered orally twice daily for 14 to 28 days, and those in both xemilofiban groups received a placebo that was identical in appearance to ticlopidine (in order to maintain the blinding). The initial dose of ticlopidine or placebo was administered 30 to 90 minutes before the performance of PTCR, with maintenance treatment initiated 6 to 8 hours after the first dose. All patients received a daily dose of 80 to 325 mg of aspirin.

Patients were evaluated 10 to 21 days and 60 days after PTCR. Subsequent monitoring for cardiac events, safety, laboratory values, concurrent medications, and compliance was performed monthly by telephone or by site visits. Cardiac end points were reported throughout the 182-day study period, regardless of compliance. Adverse events, including bleeding, were reported only if they occurred while the patient was receiving the study drug. A follow-up visit was scheduled to detect cardiac events that occurred within 30 days after the study regimen had been terminated.

Study End Points

There were two primary end points. The first was event-free survival at 182 days, with an event defined as death, nonfatal myocardial infarction, or the need for urgent revascularization on the basis of evidence of ischemia, cardiac symptoms, or both. The second primary end point was event-free survival at 182 days, with an event defined as death or nonfatal myocardial infarction.

Secondary end points included event-free survival at 30 days and at 7 months for the two sets of events noted above, the cumulative incidence of bleeding events, and survival at 30 days, 6 months, and 7 months without the need for revascularization and without other events, including rehospitalization because of unstable angina or nonhemorrhagic stroke. We also evaluated the efficacy of treatment with xemilofiban according to whether the patient received a stent.

For patients who did not have a diagnosis of myocardial infarction at the time of enrollment, the criterion for a new myocardial infarction occurring within 24 hours after PTCR was a creatine kinase MB level that was more than three times the upper limit of the normal range.[36] For patients undergoing PTCR within 24 hours after the onset of acute myocardial infarction, the criterion for the diagnosis of reinfarction within 24 hours after the procedure was defined as a creatine kinase MB level that was twice as high as the lowest elevated value before PTCR. For all patients, a myocardial infarction more than 24 hours after PTCR was defined by a creatine kinase level that was more than two times the upper limit of the normal range or the appearance of new Q waves of 0.04 second's duration with a depth of more than one quarter of the corresponding R-wave amplitude in two or more contiguous leads. When creatine kinase MB values were not available, values for total creatine kinase were used. Serum samples were collected at base line and 8, 16, and 24 hours after PTCR. Thereafter, cardiac enzymes were measured only when clinically indicated.

Urgent revascularization was defined as unanticipated revascularization (PTCR or coronary bypass surgery) performed because of unstable coronary symptoms (unstable angina or myocardial infarction) or evidence of acute, unprovoked ischemia.

Episodes of bleeding were considered moderate if they caused a drop in the hemoglobin level of at least 5 g per deciliter or a drop in the hematocrit of 15 percent or if a transfusion was required. All episodes of intracranial bleeding and bleeding that caused hemodynamic compromise and required intensive monitoring and intervention were considered severe. Episodes of mild bleeding were also recorded.

An independent clinical-events committee adjudicated all reported cardiac end points and episodes of moderate or severe bleeding. In addition, a central electrocardiographic laboratory reviewed all electrocardiograms obtained at base line and on withdrawal of the study drug. Another committee reviewed all cases of thrombocytopenia (defined as a platelet count of less than 80,000 per cubic millimeter) to determine whether they were caused by the study drug. Committee members were unaware of the treatment assignments.

Statistical Analysis

The trial was designed to have 90 percent power to detect a 25 percent reduction in the composite end point of death, nonfatal myocardial infarction, or urgent revascularization in pairwise comparisons of each xemilofiban treatment group with placebo, with a two-sided type I error of 0.025, assuming an event rate of 17.6 percent in the placebo group. Early in the trial and before unblinding, the type I error for each treatment comparison was partitioned between the two primary end points, with a type I error of 0.02 allocated to the first primary end point, and the remainder to the second primary end point.

Two interim analyses of efficacy (and more frequent reviews of safety) were conducted by an independent data and safety monitoring board with the use of symmetric O'Brien–Fleming type sequential monitoring boundaries. Analyses were prepared for the data and safety monitoring board by an independent data-analysis center. For the final analysis, the level of significance was 0.02 for the first primary end point and 0.01 for the second primary end point, with simulation used to account for repeated testing and the correlation between the test statistics for the two primary end points over the course of the trial.[37]

Cumulative event rates for each end point were estimated with the use of the Kaplan–Meier method; for composite end points, the time from randomization to the first occurrence of any component of the end point was analyzed. Comparison of each xemilofiban group with the placebo group was performed with the use of a protocol-specified Wilcoxon test for cardiac events and a log-rank test for bleeding events. Hazard ratios and 95 percent confidence intervals were estimated with the use of a Cox model. Analyses of cardiac end points were performed on an intention-to-treat basis and included all patients according to the assigned treatment and all adjudicated cardiac end points during the designated follow-up period.

TABLE 1. BASE-LINE AND PROCEDURAL CHARACTERISTICS OF THE PATIENTS.

CHARACTERISTIC*	PLACEBO (N=2414)	XEMILOFIBAN, 10 mg (N=2400)	XEMILOFIBAN, 20 mg (N=2418)
Male sex (%)	79.4	76.5	78.5
White race (%)	88.8	88.2	89.9
Age (yr)			
Median	59	59	59
Interquartile range	52–67	51–67	51–67
Weight (kg)			
Median	81.7	81.0	81.2
Interquartile range	72.6–92.3	72.0–91.9	72.2–92.1
Diagnosis at entry (%)			
Unstable angina	44.7	44.7	44.5
Stable angina	42.6	42.8	42.4
Myocardial infarction	13.7	12.5	13.1
Prior CABG (%)	9.6	10.4	10.6
High-risk criteria (%)†			
Lesion type B1 (and age >65 yr), B2, or C	56.8	55.0	55.7
Diabetes mellitus	17.9	20.3	18.0
Ejection fraction <0.30	2.0	2.1	1.9
Multivessel disease	47.4	47.6	44.8
Lesion in saphenous-vein graft	3.8	4.8	4.7
Intervention (%)†			
PTCR with stenting	71.9	70.1	71.4
PTCR without stenting	25.0	26.0	25.0
PTCR not performed	3.2	3.9	3.6
Rotational atherectomy	4.3	4.8	5.3
Use of abciximab	1.6	1.2	1.5
Heparin dose (units/kg of body weight)			
Median	118	119	118
Interquartile range	98–149	98–152	97–149
Maximal ACT (sec)			
Median	310	317‡	320‡
Interquartile range	265–356	268–377	270–374

*CABG denotes coronary-artery bypass grafting, PTCR percutaneous transluminal coronary revascularization, and ACT activated clotting time.

†The categories are not mutually exclusive.

‡P<0.001 for the comparison with the placebo group.

Other variables are reported as medians with interquartile ranges (25th and 75th percentiles), in the case of continuous variables, and as frequencies, in the case of categorical variables, with treatment-group comparisons performed with the use of the Wilcoxon test and the chi-square test, respectively. All reported P values are nominal and two-sided.

RESULTS

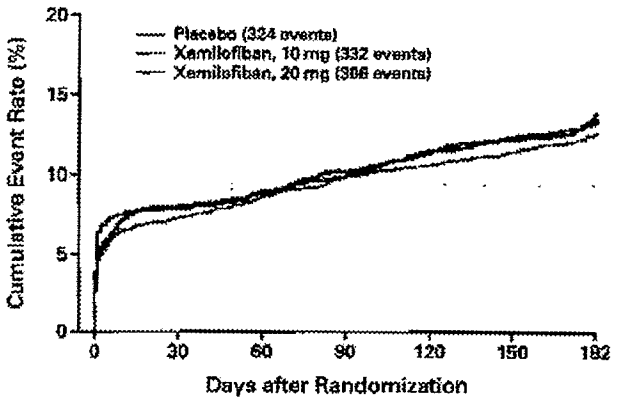
Between June 25, 1997, and April 24, 1998, a total of 7232 patients between the ages of 25 and 81 years were enrolled in the study. The average duration of follow-up was 205 days in the placebo group and the group that received 20 mg of xemilofiban and 204 days in the group that received 10 mg of xemilofiban.

The base-line characteristics of the patients are shown in Table 1. There were no significant differences among the three groups. The characteristics of the index PTCR are also shown in Table 1. Stents were implanted in 71 percent of patients, and rotational atherectomy was performed in 5 percent, with no significant differences among the groups. The median maximal activated clotting time was significantly longer in both xemilofiban groups than in the placebo group (P<0.001).

Death, nonfatal myocardial infarction, or urgent revascularization occurred within 182 days in 324 patients in the placebo group (Kaplan–Meier cumulative event rate, 13.5 percent), 332 patients in the 10-mg xemilofiban group (cumulative event rate, 13.9 percent; P=0.82 for the comparison with the placebo group; hazard ratio, 1.03; 98 percent confidence interval, 0.86 to 1.23), and 306 patients in the 20-mg xemilofiban group (cumulative event rate, 12.7 percent; P=0.36 for the comparison with the placebo group; hazard ratio, 0.94; 98 percent confidence interval, 0.78 to 1.13) (Fig. 1 and Table 2). Death or nonfatal myocardial infarction occurred within 182 days in 215 patients in the placebo group (cumulative event rate, 8.9 percent), 220 patients in the 10-mg xemilofiban group (cumulative event rate, 9.2 percent; P=0.87 for the comparison with the placebo group; hazard ratio, 1.02; 99 percent confidence interval, 0.80 to 1.31), and 199 patients in the 20-mg xemilofiban group (cumulative event rate, 8.2 percent; P=0.36 for the comparison with the placebo group; hazard ratio, 0.92; 99 percent confidence interval, 0.71 to 1.18). There were no significant differences among the three groups in either composite end point at 30 or 213 days (Table 2). Mortality rates were similar to or lower than those reported in prior studies[18]; however, there were nominally more deaths in the 10-mg xemilofiban group than in the placebo group (Table 2).

Hazard ratios for the composite end point of death, nonfatal myocardial infarction, or urgent revascularization within 182 days are shown in Figure 2 for various subgroups of patients. None of the differences between subgroups were significant. Treatment effects were similar in the stent and no-stent groups. In addition, there were no significant or clinically meaningful differences in the treatment effect according to the timing of the initial dose of the study drug (i.e., whether it was administered within 60 minutes before the performance of PTCR or earlier) or the timing of the first maintenance dose.

Analyses of myocardial infarction at various intervals after PTCR were performed to determine whether there was a period during which xemilofiban conferred a benefit. Notably, myocardial infarctions that occurred within a day after randomization or after the index procedure were less frequent in patients treated with 10 or 20 mg of xemilofiban than in those who received placebo (P=0.02 for both comparisons) (Fig. 3). Subsequently, however, there were more infarctions in both xemilofiban groups, and by 30 days, there were no significant differences between the xemilofiban groups and the placebo group (Table 2).



No. at Risk							
Placebo	2414	2220	2197	2163	2134	2110	1974
Xemilofiban, 10 mg	2400	2206	2183	2160	2126	2095	1944
Xemilofiban, 20 mg	2418	2242	2212	2178	2158	2132	2006

Figure 1. Kaplan–Meier Cumulative Event Rates for the Composite End Point of Death, Nonfatal Myocardial Infarction, or Urgent Revascularization.

The cumulative event rates in the two xemilofiban groups did not differ significantly from the rate in the placebo group.

TABLE 2. KAPLAN–MEIER CUMULATIVE EVENT RATES FOR CARDIAC END POINTS.

TIME AND EVENT	PLACEBO (N=2414)		XEMILOFIBAN, 10 mg (N=2400)			XEMILOFIBAN, 20 mg (N=2418)		
	NO. OF EVENTS	CUMULATIVE RATE	NO. OF EVENTS	CUMULATIVE RATE	P VALUE*	NO. OF EVENTS	CUMULATIVE RATE	P VALUE*
		%		%			%	
30 Days								
Death	8	0.3	20	0.8	0.02	14	0.6	0.20
Myocardial infarction	147	6.1	139	5.8	0.58	131	5.4	0.28
Urgent revascularization	71	2.9	86	3.6	0.23	64	2.6	0.49
Death or myocardial infarction	153	6.3	154	6.4	0.98	137	5.7	0.29
Death, myocardial infarction, or urgent revascularization	191	7.9	192	8.0	0.96	176	7.3	0.33
182 Days								
Death	24	1.0	40	1.7	0.04	27	1.1	0.68
Myocardial infarction	202	8.4	192	8.1	0.56	181	7.5	0.23
Urgent revascularization	166	6.9	184	7.7	0.30	158	6.6	0.59
Death or myocardial infarction†	213	8.9	220	9.2	0.87	199	8.2	0.36
Death, myocardial infarction, or urgent revascularization†	324	13.5	332	13.9	0.82	306	12.7	0.36
218 Days								
Death	35	1.6	44	1.9	0.02	30	1.3	0.55
Myocardial infarction	211	8.8	207	8.5	0.76	194	8.1	0.32
Urgent revascularization	171	7.2	189	8.0	0.29	165	7.0	0.66
Death or myocardial infarction	225	9.4	238	10.1	0.62	213	8.9	0.46
Death, myocardial infarction, or urgent revascularization	337	14.1	352	14.9	0.64	325	13.6	0.47

*P values are nominal and are for comparisons with the placebo group.

†This was a primary end point.

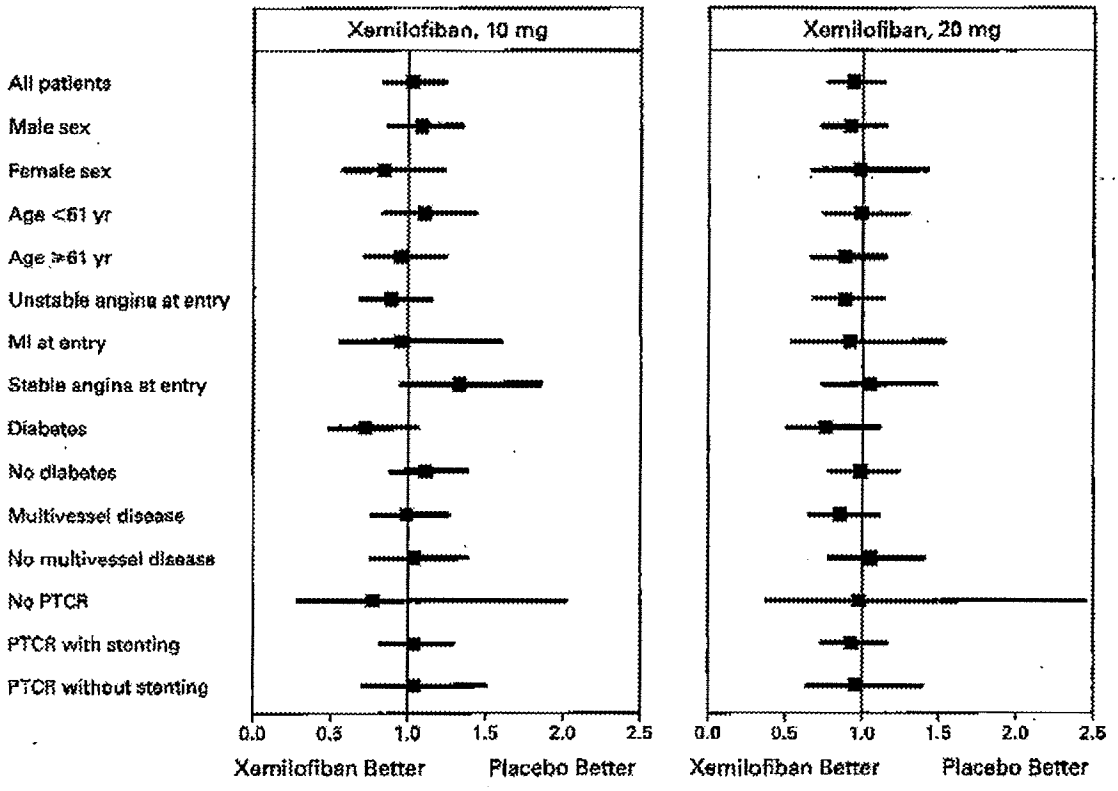


Figure 2. Hazard Ratios for the Composite End Point of Death, Myocardial Infarction, or Urgent Revascularization within 182 Days after Randomization.

The horizontal lines indicate 95 percent confidence intervals. MI denotes myocardial infarction, and PTCR percutaneous transluminal coronary revascularization.

Overall, 67.0 percent of the patients receiving placebo completed the treatment regimen, as compared with 64.2 percent of the patients receiving 10 mg of xemilofiban ($P=0.04$) and 59.4 percent of those receiving 20 mg of xemilofiban ($P<0.001$). The proportions of patients who withdrew from the study because of cardiac events were similar in the placebo, 10-mg, and 20-mg groups (10.0, 10.8, and 9.6 percent, respectively). The proportions of patients who withdrew because of episodes of bleeding (Table 3) were significantly larger in the 10-mg and 20-mg xemilofiban groups (6.1 and 11.6 percent, respectively) than in the placebo group (1.5 percent), and these differences account for the lower overall rates of completion in the xemilofiban groups.

Although a majority of the patients taking xemilofiban had bleeding, moderate or severe episodes of bleeding were infrequent (Table 3). Bleeding episodes occurred throughout the treatment period rather than predominantly in the initial period after revascularization. Thrombocytopenia (a platelet count of less than 80,000 per cubic millimeter) occurred in 0.5 percent of the patients receiving 10 or 20 mg of xemilofiban, generally in the first three or four weeks of treatment, and in 0.1 percent of the patients receiving placebo. Among the patients with thrombocytopenia, the nadir platelet count was generally less than 20,000 per cubic millimeter, and the count returned to a level of 80,000 per cubic millimeter or higher within three or four days after the study drug had been withdrawn. No deaths were attributable to thrombocytopenia.

DISCUSSION

The EXCITE trial tested the hypothesis that in patients treated with PTCR, long-term oral administration of xemilofiban, after an initial dose given before the procedure, would extend the clinical benefit of short-term glycoprotein IIb/IIIa receptor blockade previously demonstrated with abciximab, tirofiban, and eptifibatide.[39] Our finding that treatment with xemilofiban did not improve the long-term out-

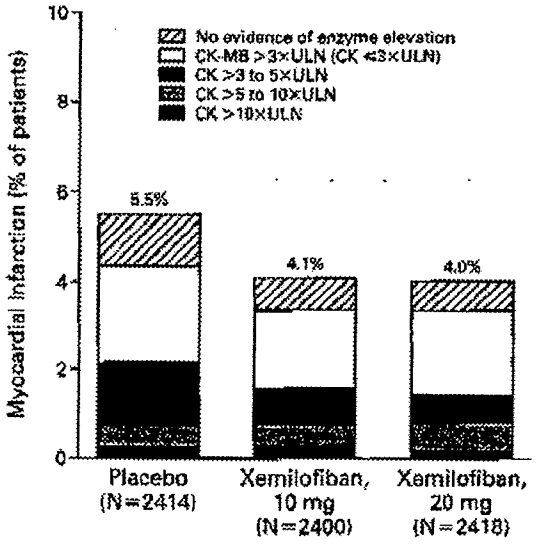


Figure 3. Myocardial Infarctions Occurring within One Day after Randomization or the Index Revascularization, According to the Creatine Kinase (CK) Level.

P=0.02 for the comparison between each xemilofiban group and the placebo group. ULN denotes the upper limit of the normal range.

come after PTCR has two possible explanations. First, this short-acting oral agent may not have had sufficient efficacy in the short term. Second, long-term use of the agent may not have had an incremental benefit. Pharmacokinetic studies have shown that 20 mg of xemilofiban provides 60 to 80 percent receptor blockade 60 to 90 minutes after oral administration.[35] Since we found no difference in outcomes according to the timing of the initial dose in relation to PTCR or the timing of the first maintenance dose, timing is an unlikely explanation for our results.

Although we did not perform systematic assays of platelet inhibition, it is possible to make inferences from other studies. Dangas et al.[40] have shown that intravenous administration of glycoprotein-receptor antagonists inhibits the generation of thrombin and prolongs the activated clotting time. In our study, the activated clotting time was significantly longer in the patients who received 10 or 20 mg of xemilofiban than in those who received placebo, suggesting that the biologic effects of xemilofiban are similar to those of other glycoprotein-receptor antagonists. More important, as with all previous trials of intravenous agents in patients undergoing PTCR, xemilofiban significantly decreased the rate of myocardial infarction in the first 24 hours after the procedure. In addition, the need for "bailout" use of abciximab was excep-

TABLE 3. EPISODES OF BLEEDING.

VARIABLE	PLACEBO (N=2414)		XEMILOFIBAN, 10 mg (N=2400)			XEMILOFIBAN, 20 mg (N=2418)		
	NO. OF EVENTS	RATE	NO. OF EVENTS	RATE	P VALUE*	NO. OF EVENTS	RATE	P VALUE*
		%		%			%	
Any bleeding†								
Within 30 days	763	32.8	1071	46.3	<0.001	1324	57.1	<0.001
Within 182 days	919	41.1	1313	59.0	<0.001	1628	72.6	<0.001
Moderate or severe bleeding†								
Within 30 days	31	1.4	75	3.3	<0.001	96	4.3	<0.001
Within 182 days	39	1.8	106	5.1	<0.001	145	7.1	<0.001
Site or sign of moderate or severe bleeding								
Groin	10	0.4	20	0.8	0.06	31	1.3	0.001
Intracranial site	1	<0.1	3	0.1	0.31	5	0.2	0.10
Drop in hematocrit or hemoglobin level	16	0.7	37	1.5	0.004	48	2.0	<0.001
Melena	0	0	19	0.8	<0.001	28	1.2	<0.001
Other gastrointestinal site	4	0.2	10	0.4	0.11	33	1.4	<0.001
Intervention due to bleeding								
Transfusion	26	1.1	76	3.2	<0.001	108	4.5	<0.001
Dose adjustment	30	1.2	129	5.4	<0.001	285	11.8	<0.001
Withdrawal of study drug	36	1.5	146	6.1	<0.001	281	11.6	<0.001
Abnormal laboratory value‡								
Hemoglobin	492	21.4	637	28.0	<0.001	691	29.9	<0.001
Hematocrit	548	23.9	648	28.8	<0.001	727	31.6	<0.001
Platelet count	98	4.3	101	4.5	0.76	133	5.8	0.02

*P values are nominal and are for comparisons with the placebo group.

†Percentages are Kaplan–Meier cumulative event rates during receipt of the study drug.

‡Data are for patients who had a value below the lower limit of the normal range at any time after enrollment. Data were available for 3299 patients in the placebo group, 2275 patients in the group given 10 mg of xemilofiban, and 2311 patients in the group given 20 mg of xemilofiban.

tionally low, and the rate of bleeding events in the early period after PTCR was higher in the active-treatment groups than in the placebo group. These findings suggest that xemilofiban had short-term biologic and clinical efficacy.

The second explanation for these results is that continued treatment with xemilofiban did not confer long-lasting protection from death, myocardial infarction, or the need for urgent revascularization. The lack of a prolonged benefit was observed both in the entire cohort of patients and in subgroups defined according to the diagnosis at enrollment, stent use or nonuse, age, sex, and interval between the initial dose of the study drug and PTCR.

The lack of long-term efficacy is unlikely to be due to an insufficient dose of xemilofiban. Blood levels of xemilofiban were sufficiently high to exert the desired antagonist effect on platelet receptors, at least intermittently, since there was a dose-dependent increase in bleeding events over the entire study period. The steep dose responses characteristic of xemilofiban pharmacodynamics and pharmacokinetics may have caused large fluctuations in the inhibition of platelet aggregation in individual patients, with variable inhibition in the study population as a whole.[35]

Lamifiban has been reported to prevent death and myocardial infarction only at intermediate plasma levels, not at lower or higher plasma levels, in patients with unstable angina.[41] Studies of platelet activation raise the possibility, which has not yet been confirmed, that at low concentrations, platelet-receptor antagonists alter the steric conformation of the glycoprotein IIb/IIIa sites and, paradoxically, enhance the thrombogenicity of these sites.[42] This may explain the higher mortality rates in the low-dose xemilofiban group. It therefore appears that lack of a long-term protective effect is the most likely explanation for the results of our trial.

Another unexpected finding was that event rates were lower than in previous trials. The rate of death, nonfatal myocardial infarction, or urgent revascularization at 30 days was 7.9 percent in our placebo group, as compared with 12.8 percent in the placebo group in the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial,[4] 11.4 percent in the placebo group in the Integrelin to Minimize Platelet Aggregation and Prevent Coronary Thrombosis (IMPACT) II trial,[11] 11.7 percent in the placebo group in the Evaluation in PTCR to Improve Long-Term Outcome with Abciximab GP IIb/IIIa Blockade (EPILOG) study,[7] and 10.8 percent in the stent group in the Evaluation of Platelet IIb/IIIa Inhibition in Stenting (EPISTENT) study.[38] Although the enzymatic criteria for diagnosing myocardial infarction were not uniform in these trials, a trend is suggested. During the period when the EXCITE trial was conducted, PTCR was evolving rapidly. Stent placement was becoming commonplace throughout the world and was used in 71 percent of the patients in the trial. New stent designs that eliminated the need for bulky delivery devices and implantation under high pressure may have lessened the trauma to the vessel wall. Angioplasty without stent placement was reserved predominantly for patients in whom the results of angioplasty were "stent-like."[26] These improvements in interventional techniques may have diminished the importance of glycoprotein IIb/IIIa receptor blockade. In addition, heparin therapy was more aggressive in our trial than in studies of abciximab. The longer activated clotting time in our study may have decreased the frequency of thrombotic or embolic complications of PTCR.

Fifty-seven percent of the patients enrolled in our trial had a diagnosis of acute myocardial infarction or unstable angina at enrollment. The lack of treatment efficacy in this subgroup suggests that the overall lack of a benefit was not due to the unintentional enrollment of low-risk patients.

In conclusion, the administration of xemilofiban immediately before and for up to six months after PTCR does not decrease the combined end point of death, nonfatal myocardial infarction, or urgent revascularization. Although treatment with xemilofiban reduces the rate of myocardial infarction by 25 percent in the first 24 hours after PTCR, it does not reduce the mortality rate initially or at six months. The value of long-term treatment with oral glycoprotein-receptor blockers thus remains unproved.

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APPENDIX

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Biodegradable implant strategies for inhibition of restenosis

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Abstract

Restenosis of coronary arteries within 6 months of angioplasty has severely limited the long-term success of this procedure. As with any procedure that involves vascular manipulation, thrombosis and stenosis due to intimal proliferation and blood vessel remodeling are the processes that interfere with prolonged patency. This review explores the latest strategies in the form of biodegradable implants designed to inhibit arterial restenosis. The devices discussed herein have potential usefulness not only in coronary artery disease but also in a broad variety of vascular procedures and settings.

Keywords: Biodegradable drug delivery systems; Restenosis; Thrombosis; Heparin; Polyanhydride; Polyvinyl alcohol

Contents

1. Introduction

1.1. The problems of thrombosis and restenosis

Acute thrombosis and delayed stenosis are potential complications of any vascular procedure. Percutaneous transluminal coronary angioplasty (PTCA) procedures have been plagued by a restenosis rate of up to 50% within 6 months [1,2]. Other vascular surgical procedures, including carotid endarterectomy, large- and small-vessel anastomoses, vascular grafts and fistulae, and tissue and organ transplants all suffer from these potential complications as well. The consequences of thrombosis and restenosis are often catastrophic, resulting in myocar-

Abbreviations: CyA, cyclosporine; PTCA, percutaneous transluminal coronary angioplasty; PVA, polyvinyl alcohol

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